REMARKS

Claims 1-45 were presented at the time of filing. In response to a restriction requirement dated October 18, 2004, Applicant elected Group I, claims 1-14 and 31-45. In response to a non-final Office Action dated February 28, 2005, claims 15-30 were cancelled. Claims 1-14 and 31-45, therefore, were pending in the application. Claims 1, 4, 7, 31, 34 and 37 are amended above. Claims 1-14 and 31-45 remain pending in the application.

The claims are amended to more clearly define the cell type suitable for practicing the methods of the present invention and to describe an additional feature of the mutant sodium channels of the invention.

Rejections under 35 U.S.C.§112, first paragraph

Claims 1-14 and 31-45 are rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the written description requirement, that is, that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. According to the Office Action, "the claims do not require that the polypeptides possess any particular conserved structure, or any other disclosed distinguished feature. Thus the claims are drawn to a genus of amino acids that is defined by a large number of amino acid substitutions." Being drawn to a genus of proteins containing a very large number of species however, is not fatal to compliance with the written description requirement where, as in the instant case, one of skill in the art can envision all the members of the genus.

The claims, as amended above, are directed to a method for assessing the potential of a compound to function as an anti-arrhythmic agent using an isolated cell transfected with a recombinant mutant Nav 1 sodium channel protein. The mutant sodium channel protein has an amino acid sequence in which one or more amino acids among the ten amino acids occurring at

the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of a mammalian Nav1 protein *differs from the amino acid in wild-type Nav1* by substitution with tryptophan, phenylalanine, tyrosine or cysteine. In other words, the mutant sodium channel protein of the invention has the same amino acid sequence as the corresponding wild-type mammalian Nav 1, **except** that one or more amino acids among the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of the mutant protein differs from the amino acid in wild-type Nav1 by substitution with one of tryptophan, phenylalanine, tyrosine or cysteine. Amino acid substitution outside of the 10 amino acid carboxy region of S6 is not contemplated by or claimed in the instant application. Thus, the number of possible mutants, albeit a very large number, is a finite number of specifically identified mutants and not an incalculable number. Because the sequence of the wild-type is known, one of skill in the art can envision every member of the genus of mutant molecules based on the description of the mutant in the specification.

Nav proteins consist of one large α-subunit which contains four homologous repeated domains (D1-D4) each with six transmembrane segments (S1-S6) (see Figure 1). The complete amino acid sequences for several isoforms of mouse, rat and human Nav 1 proteins are known and available in the NCBI database. The amino acid sequences of the four S6 regions of several rat and human isoforms is provided in the specification on pages 3 and 4. As disclosed in the specification on page 3, paragraph [0006], there is very close homology among the S6 segments of mammalian Nav proteins so far identified and that this homology extends both through species and isoforms.

As discussed above, the amino acid substitutions encompassed by the present invention are limited to a region of ten amino acids occurring at the carboxy end of the S6 segment of each of D1, D2, D3 or D4. The claimed invention does not encompass mutations, substitutions, insertions or deletions in any other portion of Nav 1.1, Nav 1.2...Nav 1.9. Furthermore, these specific 40 amino acid positions can only be substituted with one of four possible replacement amino acids: tryptophan, phenylalanine, tyrosine or cysteine. In actuality, while the number of possible mutant sodium channels contemplated by the invention is a large number, it is much

more limited than the office action would suggest. As a practical matter, one of skill in practicing the invention would seek to make the least number of substitutions necessary to obtain the activation/inactivation deficient sodium channel of the invention.

In support of its position, the previous Office Action cited University of California v. Eli Lilly for the proposition that Applicant's claims encompass a very large undisclosed genus. Applicant respectfully submits that application of the law as enunciated in Lilly is inapposite to the current invention. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. In Lilly, it was held that the written description requirement as applied to certain biotechnology patents, in which a gene material has been defined ***only*** by a statement of function or result, is not satisfied by such a statement. In Lilly, the court concluded that a claim to a microorganism containing a human insulin cDNA was not adequately described by a description of rat insulin cDNA and a statement that the invention included human insulin. In Lilly, the nucleic acid sequences for insulin of other species including human had not yet been identified.

The term "human insulin cDNA" in Lilly's claim conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. An adequate written description of genetic material, according to the Lilly court, requires "a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." In Lilly, the sequence of only one species of insulin was disclosed and because the sequence of human insulin had yet to be elucidated, there was no additional information regarding homology of the disclosed sequence with others of the claimed genus, and in particular no information with respect to human insulin. The specification in the Lilly case, therefore, did not demonstrate that the inventors had possession of human insulin cDNA.

This is quite different from the present situation. Unlike Lilly, Applicant discloses the wild-type sequence for two mammalian species, rat and human, and multiple isoforms for each species. Additionally, the specification includes comparisons of the wild-type amino acid sequences for the relevant region, i.e. the S6 transmembrane segments of D1, D2, D3 and D4 where the mutations are to be made. With minor exception, the rat and human Nav 1 sequences are identical.

The previous Office Action also cited Fiers v. Revel, Amgen v. Chugai Pharmaceutical and Fiddes v. Baird for the proposition that "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred..." That case is completely inapposite to the instant case. In Fiers, Fiers attempted to argue that conception of a previously *unknown* DNA (β-interferon) can occur if one defines it by its method of preparation. Unlike the cited case, the present invention relates to specifically identified mutants of a known protein, the complete wild-type amino acid sequences for several Nav 1 isoforms and species being known. Based on Applicant's research, the mutations contemplated by the present invention occur in a specific, well elucidated region of the Nav1 protein. Thus, the skilled artisan can easily envision what the chemical structure of the mutant sodium channel would be.

In the instant case, Applicant has more than adequately described the mutant sodium channels encompassed by the invention not, as in Lilly, in terms of function alone, but rather by providing the precise structure/sequence of the wild type molecule in conjunction with a description of the relevant regions to be substituted, i.e., the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 an D4. Furthermore, replacement of amino acids in the pertinent 10 amino acid regions is limited to substitution with only four possible replacements: tryptophan, phenylalanine, tyrosine or cysteine. Applicant respectfully submits that it is unclear how one could provide a more precise definition. Clearly, from this description, the skilled artisan could, in fact, envision the detailed chemical structure of the claimed genus of polypeptides, albeit a large one.

Therefore, in view of the fact that Applicant has identified a specific structural region of known Nav 1 proteins believed to be involved in channel activation, and has been able to demonstrate that channel activation can be modified by making very limited amino acid replacements in this region, it is believed that the specific examples of cells containing a mutant sodium channel protein provided in the specification clearly provide an adequate written description of the invention.

In view of the above remarks, the rejection under 35 U.S.C. §112, first paragraph of claims 1-14 and 31-45 based on lack of written description is believed overcome. Withdrawal of the rejection is respectfully requested.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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